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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,765	05/23/2001	Zhen-Gang Wang	9373/IH812US2	9136
7278	7590	04/20/2004	EXAMINER	
DARBY & DARBY P.C. P. O. BOX 5257 NEW YORK, NY 10150-5257			ZHOU, SHUBO	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/863,765

Applicant(s)

WANG ET AL.

Examiner

Shubo "Joe" Zhou

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2003 and 30 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-151 is/are pending in the application.
- 4a) Of the above claim(s) 25-27 and 41-150 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-24, 28-40 and 151 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 May 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 10/1/01, 10/24/03.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **Detailed Action**

### ***Election/Amendments***

1. Applicants' election, with traverse, of Group I (claims 1-24, 28-40, and 151) in the communication filed 10/9/03, is acknowledged. Applicants assert that the groups of claims in the application do not define methods or compositions which are sufficiently distinct to warrant separate examination and searches, and therefore the restriction is improper. This traverse is not found persuasive because applicants do not give reasons why the groups are not distinct and co-examination of them do not require separate searches and do not impose undue burden to the Office. It is set forth in the previous Office action mailed 9/9/03 that the groups of inventions as set forth in the action differ both physically and functionally; require different process steps, reagents and parameters, and produce different products and/or results. Consequently, these inventions have acquired a separate status in the art as a separate subject for inventive effect and are usually published separately. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Thus, examination of the invention groups together would impose an undue search burden to the Office. See pages 3-4. Thus, the restriction requirement is still deemed proper and is therefore made FINAL.

Claims 25-27, 41-150 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

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generic or linking claim. Applicant timely traversed the restriction (election) requirement in the communication filed 10/9/03.

Accordingly, claims 1-24, 28-40, and 151 are currently under examination.

### ***Information Disclosure Statement***

2. The Information Disclosure Statements filed 10/1/01 and 10/24/03 have been entered and considered. Initialed copies of the forms PTO-1449 are enclosed with this action.
3. The citations/listings of publications and/or patents in various sections of the specification such as those on pages 6 and 34 are not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

### ***Specification***

4. The specification is objected to because of the following:
5. The title of the invention is not descriptive. The elected invention is drawn to methods and systems for identifying crossover locations for the recombination of biopolymers, whereas the current title is directed to gene recombination and hybrid protein development. A new title is required that is clearly indicative of the invention to which the elected claims are directed.

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6. Applicant is reminded of the proper content of an abstract of the disclosure.

Where applicable, the abstract should include the following:

- (1) if a machine or apparatus, its organization and operation;
- (2) if an article, its method of making;
- (3) if a chemical compound, its identity and use;
- (4) if a mixture, its ingredients;
- (5) if a process, the steps.

In the instant case, the Abstract on page 113 of the specification does not give the steps of the processes claims. Revision of the content of the abstract is required on a separate sheet.

7. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, first paragraph***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-3, 5, 10, 19-21, 24, 34-35, and 38-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 2-3 recite "the particular polymer sequence" of claim 1. There are at least two particular polymer sequences in claim 1 recited, a first polymer sequence and a second polymer sequence. It is not clear which one of the sequences is meant in claims 2-3. Claim 10 is rejected because it depends from claim 2 and contains the confusing limitation.

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11. The recitation in claim 5, "the coupling matrix" of the method of claim 1, lacks clear antecedent basis. The method of claim 1 does not recite a coupling matrix. Thus, it is unclear as to what is claimed.

12. The phrase "the identification of possible cut points in the biopolymer" in claim 19 lacks clear antecedent basis. There are a plurality of biopolymers recited prior to the step, and it is not clear which one is meant by the phrase. Claims 20-21, 24, 34-35, and 38-39 are rejected because they depend from claim 19, directly or indirectly, and thus also contain the confusing phrase. Further, the meaning of the phrase "if the identified fragment has a sequence identity cut-point at the end of the fragment" recited in claim 24 is unclear.

### ***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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14. Claims 1-18, 28-33, 36-37, 40, and 151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bogarad et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 96, pages 2591-2595, 1999) in view of Panchenko et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 93, pages 2008-2013, 1996).

Claims 1-18, 28-33, 36-37, 40, and 151 are drawn to methods and computer systems for selecting a crossover location in a biopolymer sequence for recombination.

Bogarad et al. disclose a method for protein or nucleic acid molecular evolution by recombination and mutagenesis. The method comprises, inter alia, shuffling or swapping structures of folding or domains among different sequences. See page 2592 and Figure 1. Such swapping is interpreted as recombination. The method also comprises generating a plurality of different mutant sequences, which is interpreted as being the data structure of the instant claims, and applying energy function as selection criteria for identifying optimal sequences. The energy function includes secondary structure subdomain energies and subdomain-subdomain interaction energies. The energy function also considers amino acid side chain interactions. See page 2591, right column, and page 2592, left column. Bogarad et al., however, do not explicitly teach how the sites or locations of the domains or structures for swapping/recombination, i.e. the boundaries of the swapped structures or domains, are selected.

Panchenko et al. disclose a method and computer algorithm for identifying the boundaries of folding structures, referred to as foldons in a protein sequence. The method employs an energy function defined as  $\Theta$ , which is a measure of relative

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foldability of protein segments. Such a folding of protein segments is interpreted as comprising interactions of amino acid residues in the segments to form the folded structure. See page 2009. The method of identifying foldon boundaries comprises cutting a polypeptide chain after a certain residue  $j$ , and calculating the average  $\Theta$  value of N-terminal (from the first residue to residue  $j$ ) and C-terminal (from residue  $j$  to the last residue). Then the cleavage point is moved along the chain one residue at a time and the average  $\Theta$  value is calculated. The position of the first residue where a local maximum of  $\Theta$  is obtained is the boundary of the first foldon. Any average  $\Theta$  value below this maximum means weakened interactions between units. See page 2009. A higher  $\Theta$  indicates higher foldability of segments, i.e. interactions, and it is interpreted as having a lower disruption of the foldon. Further, every sequence resulted from cleavage at a certain residue is interpreted as a crossover mutant. Panchenko et al. state that foldons correlate well with structural modules/domains, which can fold independently, can be rearranged through genetic engineering, and in some cases have been shuffled during natural recombination. See page 2008.

One of ordinary skill in the art would have been motivated by Panchenko et al. to modify the method of Bogarad et al. to use the method by Panchenko for identifying the boundaries of foldons or domains in order to determine precisely the crossover locations for recombination of multiple sequences to achieve finer control for the recombination process.

As to the claims that require that coupling interactions among residues be identified by coupling matrix, absent a clear definition for the phrase in the specification,



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Fig. 1 of Panchenko et al. is interpreted as being a coupling matrix because it shows the foldability values, i.e. the values for interaction of residues to form a folded structure, for each linear residue of a polypeptide sequence.

As to the claims that require different values for the threshold for the crossover disruption, i.e. the  $\Theta$  value by Panchenko et al., since different foldons have different  $\Theta$  values depending on the sequence, as shown in Fig. 1 of Panchenko et al., it would have been obvious to one of ordinary skill in the art that for different sequences and depending on the particular parent sequences and the particular sequences to be created through recombination, different thresholds for the  $\Theta$  value would have been used.

15. Claims 19-24, 34-35, 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bogarad et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 96, pages 2591-2595, 1999) in view of Panchenko et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 93, pages 2008-2013, 1996), as applied to claims 1-18, 28-33, 36-37, 40, and 151 above, further in view of Jonsson et al. (Nucleic Acids Research, Vol. 21, pages 733-739, 1993).

Claims 19-24, 34-35, 38-39 are drawn to methods and computer systems executing the methods for selecting a crossover location for recombination.

As applied to claims 1-18, 28-33, 36-37, 40, and 151 above, Bogarad et al. and Panchenko et al. disclose methods and systems for recombination and for determining the boundaries of folding structures, which can be served as crossover locations for

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recombination. However, Bogarad et al. and Panchenko et al. do not explicitly teach that the crossover mutants are generated by aligning a plurality of polymer sequences, identifying possible cut points and generating crossover mutants.

Jonsson et al. disclose a method of creating new promoter structures using a quantitative sequence-activity model (QSAM). Jonsson et al. aligned 25 promoter sequences, analyze the strength of each residue relative to the overall promoter strength and identified two new sequences based on the alignments and strength analysis. See page 734, Table 1, and page 736, Figs 1-3. The new sequences created PLS1 and PLS2 have the highest promoter activity. While Jonsson et al. do not explicitly recite the term recombination, it would have been obvious to one of ordinary skill in the art that the new promoter sequences predicted, PLS1 and PLS2, are produced, in silico, by recombining the 25 parental sequences through crossovers (see Table 1), and these are considered as crossover mutants. Laboratory tests show that PLS1 and PLS2 exhibits higher biological activity than all the 25 parental sequences.

One of ordinary skill in the art would have been motivated by Jonsson et al. to modify Bogarad et al. and Panchenko et al. to use sequence alignments coupled with strength analysis, to find crossover mutants that would have the highest biological activity.

### ***Double Patenting***

16. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or

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discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

17. Claims 1-24, 28-40, and 151 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-24, 28-40, and 151 of US copending application 10/016,668, filed 10/26/01. This is a provisional double patenting rejection. The invention in every one of claims 1-24, 28-40, and 151 of the instant application is identical in scope compared to the corresponding claims of 1-24, 28-40, and 151 of US copending application 10/016,668. Even the wordings are identical.

### **Conclusion**

16. No claim is allowed.


17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on 571-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

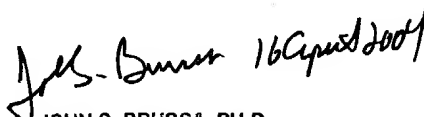
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Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst William Phillips whose telephone number is 571-272-0548, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shubo (Joe) Zhou, Ph.D. 

Patent Examiner

  
JOHN S. BRUSCA, PH.D.  
PRIMARY EXAMINER